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| 10/821,813 | 04/08/2004 | Thomas A. Boyd | P0453.70112US01 | 9059 |

7590 09/14/2007
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| EXAMINER |
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SPIVACK, PHYLLIS G

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| ART UNIT | PAPER NUMBER |
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1614

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09/14/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/821,813

Applicant(s)

BOYD ET AL.

Examiner

Phyllis G. Spivack

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 2, 4-10, 12, 13, 33-37, 40, 48-50, 71-75, 78, 79, 89-92, 84, 97-102, 105, 106, 121 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 14-32, 38, 39, 43, 45, 51-70, 76, 77, 82-85, 88, 93, 95, 96, 103, 104 and 107-121 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2-23-07; 7-2-07.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims pending in the application are 1,11,14-32,38,39,43,45,51-70,76,77,82-85,88,93,95,96,103,104 and 107-121.

Applicants' Amendment filed July 2, 2007 is acknowledged. Claims 3, 41, 42, 44, 46, 47, 80, 81, 86 and 87 are canceled. New claims 115-121 are added. Claims 2, 4-10, 12, 13, 33-37, 40, 48-50, 71-75, 78, 79, 89-92, 84, 97-102, 105 and 106 remain withdrawn from consideration. Accordingly, claims 1, 11, 14-32, 38, 39, 42, 44-5, 51-70, 76, 77, 82-85, 88, 93, 5, 96, 103, 104 and 107-121 are now under consideration.

Information Disclosure Statements filed February 23, 2004 and July 2, 2007 are acknowledged and have been reviewed to the extent a publication date is provided. Co-pending applications, S.N. 11/441452 and 11/441395, are further noted.

A complete list of co-pending and related applications for the present inventors is requested when responding to this Office Action.

Applicants' arguments have been fully considered and are persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim 121 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative. See MPEP § 608.01(n). Accordingly, the claim 121 has not been further treated on the merits.

Claim 111 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 111 recites the limitation "a pharmaceutical preparation." There is insufficient antecedent basis for this limitation in claim 108 from which claim 111 depends.

Further, Applicants have failed to define the invention properly in that claim 111 is dependent from two other claims.

Claims 1, 11, 14-32, 38, 39, 42, 43, 51, 56-70, 76, 77, 113 and 115 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite treating irritable bowel syndrome (IBS) comprising administering methylnaltrexone, and, in particular, various subsets of patient populations, various symptoms of IBS and administration of multiple drug therapy. Passages from The Merck Index are provided to show the state of the art with respect to various subsets of patient populations (page 313), various symptoms of IBS (pages 312-313) and administration of multiple drug therapy (pages 314-315). There is insufficient written basis for the subject matter of claims 1, 11, 14-32, 38, 39, 42, 43, 51, 56-70, 76, 77, 113 and 115. This is a Written Description rejection.

Signs and symptoms of IBS include pain, abdominal distention and abnormal bowel function. There are two major clinical types of IBS: constipation-predominant and diarrhea-predominant. Men, women and children are known to present distinct signs and symptoms and to respond to medications differently. Drug therapy is

supportive and palliative and includes increasing dietary fiber, anticholinergic drugs and specific agents to treat either diarrhea or constipation.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

Applicants' disclosure is entirely silent with respect to the administration of methylnaltrexone in a treatment modality for irritable bowel syndrome. There is no description of an administration regimen directed to the distinct subsets of patient populations, to the various symptoms of IBS and of multiple drug therapy. The present specification merely describes dosage formulations. Treatment regimens are prophetic. Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art, particularly with respect to dosing regimens that would be required as, particularly, in the case of regurgitation in an infant, or in the case of psychogenic vomiting. The disclosure lacks sufficient written description for all claimed limitations. No working examples are provided that would describe to one of ordinary skill in the art an embodiment that meets all the limitations of the claims. Sufficient guidance to support predictable operability of the invention to one of ordinary skill in the art is absent.

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The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 88, 93, 95, 96, 103, 104, 107-114 and 116-121 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-29, 32, 33 and 39-44 of copending Application No. 11/441452. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to pharmaceutical compositions comprising methylalntrexone, optionally in combination with other therapeutic agents, as well as in the same dosage forms that are recited in the present claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 11, 14, 16-18, 27, 29, 31, 43, 45, 51-55, 57-59, 82-85, 103, 104, 107, 108, 111 and 116 are rejected under 35 U.S.C. 102(a) as being anticipated by Levine, J.D., US 2004/0180916.

Levine teaches the administration of the specific μ opioid antagonist methylnaltrexone in combination with a κ -opioid receptor agonist to treat pain associated with IBS. Therefore, as required by instant claims 29 and 31, an opioid agonist is simultaneously administered to a patient. See, for example, page 18, paragraph [0120], or, *inter alia*, claim 154, page 34. No occurrence of calcium or salts thereof is noted in the Levine document. No restriction is noted among male, female or child patients. The open language of the present claims allows for the inclusion of any number of additional active agents. Benzodiazepines (antidepressants) are included among those κ -opioids contemplated. See, for example, claim 148, as required by instant claims 30, 32, 70, 88, 110 and 115. Psychological stress and anxiety are factors in the exacerbation of IBS, and administration of a benzodiazepine, an anti-anxiety agent, may be a component of therapy for IBS. As required by instant claims 11, 14, 52-55, 103, 104 and 107, various dosage forms are disclosed on pages 16-18. As required by instant claim 55, direct mucosal administration is disclosed on page 34, claim 154. As required by instant claim 52-54 and 104, enteric-coated formulations and sustained-release formulations are disclosed on pages 16, paragraph [0103], and page 18, paragraph [0116]. As required by instant claims 108 and 110, pharmaceutical kits (with

instructional materials) are described on page 1, paragraph [0003], and on page 25, paragraphs [0159] and [0160]. Dosage ranges, generally, 0.02 mg to 8 mg, as required by instant claims 82-84, are taught by Levine on page 6, paragraphs [0037] and [0038].

Claims 1, 11, 14-27, 29-32, 38, 39, 42, 44-5, 51-68, 70, 76, 77, 82-85, 88, 93, 5, 96, 103, 104, 107, 108 and 110-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine, J.D., US 2004/0180916, in view of The Merck Manual, and De Schryver et al., Scand. J. Gastroenterology.

Levine teaches the administration of the specific μ opioid antagonist methylnaltrexone in combination with a κ -opioid receptor agonist to treat pain associated with IBS. Therefore, as required by instant claims 29 and 31, an opioid agonist is simultaneously administered to a patient. See, for example, page 18, paragraph [0120], or, *inter alia*, claim 154, page 34. No occurrence of calcium or salts thereof is noted in the Levine document. No restriction is noted among male, female or child patients. The open language of the present claims allows for the inclusion of any number of additional active agents. Benzodiazepines (antidepressants) are included among those κ -opioids contemplated. See, for example, claim 148, as required by instant claims 30, 32, 70, 88, 110 and 115. Psychological stress and anxiety are factors in the exacerbation of IBS and administration of a benzodiazepine, an anti-anxiety agent, may be a component of therapy for IBS. As required by instant claims 11, 14, 52-55, 103, 104 and 107, various dosage forms are disclosed on pages 16-18. As required by instant claim 55, direct mucosal administration is disclosed on page 34, claim 154. As required by instant claim 52-54 and 104, enteric-coated formulations and sustained-

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release formulations are disclosed on pages 16, paragraph [0103], and page 18, paragraph [0116]. As required by instant claims 108 and 110, pharmaceutical kits (with instructional materials) are described on page 1, paragraph [0003], and on page 25, paragraphs [0159] and [0160]. Dosage ranges, generally, 0.02 mg to 8 mg, as required by instant claims 82-84, are taught by Levine on page 6, paragraphs [0037] and [0038]. Levine fails to distinguish various subsets of patient populations, various symptoms of IBS and administration of additional drugs that are 5-HT₄ agonists.

However, The Merck Index teaches various subsets of patient populations (page 313), various symptoms of IBS (pages 312-313) and administration of multiple drug therapy (pages 314-315). Signs and symptoms of IBS include pain, abdominal distention and abnormal bowel function. There are two major clinical types of IBS: constipation-predominant and diarrhea-predominant. Men, women and children are known to present distinct signs and symptoms and to respond to medications differently. Drug therapy is supportive and palliative and includes increasing dietary fiber, anticholinergic drugs and specific agents to treat either diarrhea or constipation. Abdominal bloating, pain and distention, and abnormal stools characterize IBS.

Levine fails to teach administration of methylnaltrexone with an additional irritable bowel syndrome therapeutic agent. However, De Schryver teaches the administration of the selective 5HT₄ agonist tegaserod, as required by instant claims 76, 77, 85, 93, 95, 96, 110, 112-114.

As disclosed by The Merck Index, combination drug therapy in the treatment of IBS is conventional.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack
Phyllis G. Spivack
Primary Examiner
Art Unit 1614
PHYLLIS SPIVACK
PRIMARY EXAMINER

September 12, 2007